AMENDMENTS TO THE SPECIFICATION:

Please amend the paragraph that begins on page 10, line 15 of the Substitute Specification filed on June 17, 2002 as follows:

Another object of the invention is a protein or a peptide vaccine to be used in humans, prophylactic or therapeutic against AIDS, AIDS-associated tumors and HIV-associated syndromes and symptoms and comprised of recombinant wildtype Tat protein or its mutants (~~Seq. 1-5~~ SEQ ID NOS:1, 3, 5, 7 and 9), expressed and purified as described, or wild-type or mutated Tat peptides (~~Seq.~~ Pep. 1-7, SEQ ID NOS:11-17, respectively), administered alone or conjugated with T-helper tetanus toxoid epitope or other T-helper epitopes.

Please amend the paragraph that begins on page 10, line 25 of the Substitute Specification filed on June 17, 2002 as follows:

Another object of the invention is a vaccine as described above, in combination with recombinant proteins of ~~immuno-modulant~~ immuno-modulant cytokines like IL-12, IL-15 or others molecules or part of these, capable of increasing the antiviral immune response, or a vaccine constituted by Tat/IL-12, Tat/IL-15 or Tat/other fusion proteins, or part of these, capable of increasing the antiviral immune response. Another object of the invention is a DNA vaccine, to be administered in humans, prophylactic or therapeutic, against AIDS, AIDS-associated tumors and HIV-related syndromes and symptoms, constituted by vectors coding for wild-type Tat or its mutants (~~Seq. 1-5~~ SEQ ID NOS:1, 3, 5, 7 and 9), or part of these, inserted in the expression plasmid vector pCV0 or other vectors.

Please amend the paragraph that begins on page 24, line 21 of the Substitute Specification filed on June 17, 2002 as follows:

Many difficulties have been encountered in the past to purify and maintain the biological activity of the Tat protein owing to the easiness to oxidate, aggregate and lose activity. This is due to the high amounts of cysteine residues which can form intra- and inter-molecular bonds, thus modifying the conformation of the native protein (Ref. 159, 41). The cDNA or the tat gene (~~Seq. 1~~ SEQ ID NO:1, example 2), which has been cloned in the pL-syn vector, provided by Dr. J. F. DeLamarter and B. Allet (Glaxo Institute for Molecular Biology S.A., Ginevra, Svizzera), has been used for the expression of the protein in E.Coli.

Please amend the paragraph that begins on page 36, line 7 of the Substitute Specification filed on June 17, 2002 as follows:

The sequence of the tat insert and of the mutants selected for the vaccination is reported hereinafter. A series of tat mutants is described prepared by 1) substitution of a base to obtain an amino ~~acidic~~ acid substitution and 2) deletion of a base to obtain a deletion of the correspondent amino acids. The substitutions and deletions were obtained by site direct mutagenesis. The sequences of the wildtype tat gene and of the tat gene mutants, hereinafter reported, were inserted in the pCV0 plasmid vector as described above.

Please amend the paragraph that begins on page 36, line 14 of the Substitute Specification filed on June 17, 2002 as follows:

With ~~Seq. 1~~ SEQ ID NO:1 it is intended the HIV-1 tat gene sequence, from BH-10 clone and its derived protein (SEQ ID NO:2). With ~~Seq. 2~~ SEQ ID NO:3 it is intended the cys22 mutant sequence (and its derived protein, SEQ ID NO:4), represented by a substitution of ~~Timine~~ Thymine (T) nucleotide in position ~~66~~ 64 starting from the 5' end with the Guanine (G) nucleotide. This substitution originates, in the derived amino ~~acidic~~ acid sequence, a substitution of a Cysteine (C in one letter code) in position 22 at the amino-terminal end, with a Glycine (G in one letter code). With ~~Seq. 3~~ SEQ ID NO:5 it is intended the lys41 mutant sequence (and its derived protein, SEQ ID NO:6), represented by a substitution of the ~~Timine (T)~~ Adenine (A) nucleotide in position ~~123~~ 122 from the 5' end with the Cytosine (C) nucleotide. This substitution originates, in the derived amino ~~acidic~~ acid sequence, a substitution of a Lysine (K in one letter code) in position 41 from the amino-terminal end, with a Threonine (T in one letter code). With ~~Seq. 4~~ SEQ ID NO:7 it is intended a sequence of the RGD mutant (and its derived protein, SEQ ID NO:8), represented by the deletion of the nucleotide sequence CGAGGGGAC, from nucleotide 232 to nucleotide 240, starting from the 5' end of the wild-type gene. This gives a deletion of the amino acids Arginine-Glycine-Aspartic acid (RGD in one letter code) in the positions 78-80 from the amino-terminal end. With ~~Seq. 5~~ SEQ ID NO:9 it is intended a sequence of the double lys41-RGDΔ mutant (and its derived protein, SEQ ID NO:10), originated by the combination of the above described mutants.

Please amend the paragraph that begins on page 37, line 11 of the Substitute Specification filed on June 17, 2002 as follows:

Cys22 mutant nucleotide sequence SEQ. ID. NO. 3

5'ATGGAGCCAGTAGATCCTAGACTAGAGCCCTGGAAGCATCCAGGAAGTCA
GCCTAAAACTGCT**G**GTACCAATTGCTATTGTAAAAAGTGTTGCTTTCATTGCCA
AGTTTGTTTCATAACAAAAGCCTTAGGCATCTCCTATGGCAGGAAGAAGCGG
AGACAGCGACGAAGACCTCCTCAAGGCAGTCAGACTCATCAAGTTCTCTAT
CAAAGCAGCCCACCTCCCAATCCCGAGGGGACCCGACAGGCCCGAAGGAAT
AG 3'

Please amend the paragraph that begins on page 37, line 18 of the Substitute Specification filed on June 17, 2002, and amended in the Response to Office Action filed on November 8, 2002, as follows:

Amino ~~acidic~~ acid sequence SEQ. ID. NO.4

NH2-MEPVDPRLEPWKHPGSQPKTAGTNCYCKKCCFHCQVCFITKA
LGISYGRKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGDPTGPKE-COOH

Please amend the paragraph that begins on page 37, line 21 of the Substitute Specification filed on June 17, 2002, and amended in the Response to Office Action filed on November 8, 2002, as follows:

Lys41 nucleotide sequence SEQ. ID. NO. 5

5'ATGGAGCCAGTAGATCCTAGACTAGAGCCCTGGAAGCATCCAGGAAGTCA
GCCTAAAACTGCTTGTACCAATTGCTATTGTAAAAAGTGTTGCTTTCATTGCCA
AGTTTGTTTCATAACAA~~AC~~CAGCCTTAGGCATCTCCTATGGCAGGAAGAAGCGG
AGACAGCGACGAAGACCTCCTCAAGGCAGTCAGACTCATCAAGTTTCTCTAT
CAAAGCAGCCCACCTCCCAATCCCGAGGGGACCCGACAGGCCCGAAGGAAT
AG 3'

Please amend the paragraph that begins on page 37, line 28 of the Substitute Specification filed on June 17, 2002, and amended in the Response to Office Action filed on November 8, 2002, as follows:

Amino ~~acidic~~ acid sequence SEQ. ID. NO. 6

NH2-MEPVDPRLEPWKHPGSQPKTACTNCYCKKCCFHCQVCFIXALG
ISYGRKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGDPTGPKE-COOH

Please amend the paragraph that begins on page 38, line 6 of the Substitute Specification filed on June 17, 2002, and amended in the Response to Office Action filed on November 8, 2002, as follows:

Amino ~~acidic~~ acid sequence SEQ. ID. NO. 8

NH2-MEPVDPRLEPWKHPGSQPKTACTNCYCKKCCFHCQVCFITKALG
ISYGRKKRRQRRRPPQGSQTHQVSLSKQPTSQSPTGPKE-COOH

Please amend the paragraph that begins on page 38, line 9 of the Substitute Specification filed on June 17, 2002, and amended in the Response to Office Action filed on November 8, 2002, as follows:

Lys41-RGDΔ mutant nucleotide sequence SEQ. ID. NO. 9

5'ATGGAGCCAGTAGATCCTAGACTAGAGCCCTGGAAGCATCCAGGAAGTCA
GCCTAAAACTGCTTGTACCAATTGCTATTGTAAAAAGTGTTGCTTTCATTGCCA
AGTTTGTTTCATAACAA~~AC~~CAGCCTTAGGCATCTCCTATGGCAGGAAGAAGCGG
AGACAGCGACGAAGACCTCCTCAAGGCAGTCAGACTCATCAAGTCTCTAT
CAAAGCAGCCCACCTCCCAATCCCCGACAGGCCCGAAGGAATAG 3'

Please amend the paragraph that begins on page 38, line 15 of the Substitute Specification filed on June 17, 2002 as follows:

Amino ~~acidic~~ acid sequence SEQ. ID. NO. 10

NH2-MEPVDPRLEPWKHPGSQPKTACTNCYCKKCCFHCQVCFITTALG
ISYGRKKRRQRRRPPQGSQTHQVSLSKQPTSQSPTGPKE-COOH

Please amend the paragraph that begins on page 38, line 19 of the Substitute Specification filed on June 17, 2002 as follows:

The DNA molecules for the inoculation of animals are inserted in the 6.4 kb pCV0 plasmid vector (Ref. 5). This plasmid comprises two SV40 replication origins, the major late promoter of the adenovirus (AdMLP) and the splicing sequences of the adenovirus and of the mice immunoglobulin genes, the cDNA of mice dihydrofolate-reductase gene (dhfr) and the SV40 polyadenilation signal. The site for the Pstl restriction enzyme is located at the 3' of the AdMLP, and represents the site in which the exogenous gene of interest is cloned. The tat gene cDNA (261 base pairs) (~~Seq. 1~~ SEQ ID NO:1, example 2) of HIV-1 was derived from the HIV-1 BH10 clone (Ref. 126) and coded for a 86 amino acid-long protein. The ~~pCV-Tat~~

pCV0-Tat vector (Ref. 5) was obtained by cloning the cDNA in the pCV0 PstI site, driven by the AdMLP. The choice of this vector is based on that the AdMLP induced a higher expression and release of Tat, with respect to other eukariotic promoters, such as, for instance, the immediate early region promoter of the cytomegalovirus (CMV) as demonstrated by Ensoli et al. (Ref. 41), and reported in Table 3.

Please amend the paragraph that begins on page 40, line 11 of the Substitute Specification filed on June 17, 2002 as follows:

The pCV0 vector is utilized also for the expression of HIV-1 nef, rev and gag genes and of the genes coding for IL-12 and IL-15 cytokines. The cDNAs of nef (618 base pairs, NL43 strain) (Ref. 112), rev (348 base pairs, strain NL43) (Ref. 95) and the gag genes (1500 base pairs, strain NL43) (Ref. 95), or the cDNAs of IL-I2 (Ref. 165) or IL-15 genes (Ref. 56) are amplified by polymerase chain reaction technique (PCR) by using specific primers complementary to the first 15 nucleotides of 5' region (primer forward) (~~Seq. P1, P3, P5, P7, P9~~ SEQ ID NO:18, 20, 22, 24, or 26) or to the last 15 nucleotides of 3' region of the gene (primer reverse) (~~Seq. P2, P4, P6, P8, P10~~ SEQ ID NO:19, 21, 23, 25, or 27). Moreover, each primer, both forward and reverse, comprises the sequence for the restriction PstI enzyme to consent the cloning of the amplified product into the pCV0 vector. After cloning, the sequence of the inserted genes is controlled by DNA sequencing. The pCV0 vector is used also for the Tat co-expression with other viral genes of HIV-1 (rev, nef or gag) or with the IL-12 or IL-15 cytokine-coding genes. To this end the cDNA of the HIV-1 tat gene of 261 base pairs (~~Seq. 1~~ SEQ ID NO:1, example 2) is amplified by PCR with a primer forward including the sequence for the PstI restriction enzyme (~~Seq. P11~~ SEQ ID NO:28) and a primer reverse complementary to the last 15 nucleotides of the tat gene (~~Seq. P12~~ SEQ ID NO:29). The viral genes (rev, nef or gag) or the genes coding for the IL-12 or IL-15 cytokines are amplified by a primer forward which includes also a sequence of 15 bases complementary to the tat 3' region, permitting the gene being in frame with the tat gene (~~Seq. P13, P14, P15, P16, P17~~ SEQ ID NO:30, 31, 32, 33, or 34), and a primer reverse including the sequence for the PstI restriction enzyme (~~Seq. P2, P4, P6, P8, P10~~ SEQ ID NO:19, 21, 23, 25, or 27). Afterwards, a third PCR reaction is performed in which the DNA template is represented by the amplified products of the tat gene and of the gene of interest. The primer forward is represented by the primer utilized to amplify tat (~~Seq. P11~~ SEQ ID NO:28) and the primer reverse by the one utilized in amplifying the gene of interest (~~Seq. P2, P4, P6, P8, P10~~

SEQ ID NO:19, 21, 23, 25, or 27). The amplified tat/gene of interest is purified with agarose gel, digested with PstI and cloned in pCV0. After cloning, the sequence of the inserted genes is controlled by DNA sequencing, while the protein expression is determined by means of transfection as described above (Ref. 41).

Please amend the paragraph that begins on page 41, line 10 of the Substitute Specification filed on June 17, 2002 as follows:

The sequences of the above mentioned primers are:

~~Seq. P1.~~ Primer forward Rev: 5'ATGGCAGGAAGAAGC3' **SEQ. ID. NO. 18**

~~Seq. P2.~~ Primer reverse Rev: 5'CTATTCTTTAGTTCC3' **SEQ. ID. NO. 19**

~~Seq. P3.~~ Primer forward Nef: 5'ATGGGTGGCAAGTGG3' **SEQ. ID. NO. 20**

~~Seq. P4.~~ Primer reverse Nef: 5'TCAGCAGTCCTTGTA3' **SEQ. ID. NO. 21**

~~Seq. P5.~~ Primer forward Gag: 5'ATGGGTGCGAGAGCG3' **SEQ. ID. NO. 22**

~~Seq. P6.~~ Primer reverse Gag: 5'TTATTGTGACGAGGG3' **SEQ. ID. NO. 23**

~~Seq. P7.~~ Primer forward IL-12: 5'ATGTGGCCCCCTGGG3' **SEQ. ID. NO. 24**

~~Seq. P8.~~ Primer reverse IL-12: 5'TTAGGAAGCATTCAG3' **SEQ. ID. NO. 25**

~~Seq. P9.~~ Primer forward IL-15: 5'ATGAGAATTTCGAAA3' **SEQ. ID. NO. 26**

~~Seq. P10.~~ Primer reverse IL-15: 5'TCAAGAAGTGTTGAT3' **SEQ. ID. NO. 27**

~~Seq. P11.~~ Primer forward Tat: 5'ATGGAGCCAGTAGAT3' **SEQ. ID. NO. 28**

~~Seq. P12.~~ Primer reverse Tat: 5'CTATTCCTTCGGGCC3' **SEQ. ID. NO. 29**

~~Seq. P13.~~ Primer forward Tat/Rev: 5'GGCCCGAAGGAAATGGCA GGAAGAAGC3' **SEQ. ID. NO. 30**

~~Seq. P14.~~ Primer forward Tat/Nef: 5'GGCCCGAAGGAAATGGGT GGCAAGTGG3' **SEQ. ID. NO. 31**

~~Seq. P15.~~ Primer forward Tat/Gag: 5'GGCCCGAAGGAAATGGGTGCG AGAGCG3' **SEQ. ID. NO. 32**

~~Seq. P16.~~ Primer forward Tat/IL-12: 5'GCCCGAAGGAAATGTGGC CCCCTGGG3' **SEQ. ID. NO. 33**

~~Seq. P17.~~ Primer forward Tat/IL-15: 5'GGCCCGAAGGAAATGAGAAT TTCGAAA3' **SEQ. ID. NO. 34**

Please replace the sequence listing filed on November 13, 2002 in the application with the Substitute Sequence Listing submitted herewith.